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Enhancement of dissolution rate of etoricoxib through solid dispersion technique

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ABSTRACT

Etoricoxib, a non-steroidal anti-inflammatory drug, is used to Osteoarthritis, Rheumatoid arthritis and Acute Gouty arthritis. Etoricoxib is practically insoluble in water; hence present study was carried out to enhance dissolution properties of Etoricoxib through the preparation of Solid Dispersions using PEG 6000 as carrier at various proportions by using different techniques like Physical mixtures, Kneading Method and Solvent Evaporation Method. The drug release profile was studied in 0.1N HCl containing 1 % SLS. U.V. Spectrophotometric method was selected for assay as well as in-vitro dissolution studies at 234nm. All the solid dispersions exhibited superior dissolution than pure drug. The drug dissolution studies followed first order kinetics. Solvent evaporation method was found to be superior to other methods.

Key words: Solid dispersion, Etoricoxib, Physical mixtures, Kneading method, Solvent evaporation method.

INTRODUCTION

Etoricoxib (Dallob et al., 2003). (EXB) 5-Chloro-2-[6 methyl pyridine-3-yl]-3-[4-mehtyl sulphonyl phenyl] Pyridine a non steroidal anti inflammatory drug (NSAID) has been indicated for various painful indications and proved as effective as other NSAIDS with lower indication of gastrointestinal adverse effects and thus, resulted in a greater compliance with treatment. Etoricoxib is practically insoluble in water. The rate of dissolution can be increased by increasing the surface area of available drug by various methods like Micronization, Complexation and Solid dispersion (Martin et al., 1993). (SD). Hence, an attempt was made to improve the dissolution characteristics using the solid dispersion technologies. Among various approaches to improve the dissolution rate of poorly soluble drugs, the preparation of solid dispersions has often proved to be successful (Swarbrick et al., 2002; Leunner et al., 2000; Brahmanekar et al., 2005; Chiou et al., 1969; Chiou et al., 1971). Nifedipine (Vippagunta et al., 2002). Meloxicam (Malleshwar rao et al., 2008). lansoprazole (Mamatha et al., 2008). Valdecoxib (Patel et al., 2006). Aceclofenac (Kamal et al., 2002). Carbamazepine (Prajapati et al., 2007). Glimipiride (Srinivas et al., 2008). Etoricoxib (Bhanubhai et al., 2006). Various hydrophilic carries, such as poly ethylene glycols (Liu et al., 2005). Polyvinyl pyrrolidone (Sethi et al., 2004). Sugars (Loyd et al., 2006). Urea (Chiou et al., 2006). Have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs. In the present work, solid dispersions of Etoricoxib with PEG 6000 were prepared in different drug: carrier ratios (1:1, 1:3, 1:6, 1:9) with different techniques like physical mixing (PM), solvent evaporation (SE) and kneading method (KM), to improve solubility and dissolution characteristics. U.V. Spectrophotometric method was selected for assay as well as

in-vitro dissolution studies at 234 nm in 0.1N HCl containing 0.75% SLS. The dissolution profile of best formulation i.e. drug: PEG 6000 (1:6) solvent evaporation method showed maximum dissolution rate. The increased in dissolution rate of the drug may be due to increased wettability, hydrophilic nature of the carrier and also possibility due to reduction in drug crystallinity.

MATERIALS AND METHODS

Etoricoxib was procured from Aurobindo Pharmaceuticals private limited; Hyderabad, Dichloromethane, Methanol purchased from Qualigens fine chemicals Mumbai, Polyethylene glycol 6000 Purchased from S. D fine chemicals Ltd, Mumbai and all other materials used were of pharmaceutical grade.

Preparation of physical mixtures

Physical mixtures were prepared by simple blending of accurately weighed quantities of drug (s) and carrier (s) sifted through sieve # 100 in a closed glass bottle. The powder was then stored in a desiccator.

Preparation of solid dispersion

Kneading method:

The Weighed quantities of drug and carrier were triturated in a glass mortar with a small volume of methanol. The thick slurry was kneaded for 45 mins and then dried at 50°C to constant weight. The dried mass was Pulverized and sifted through Sieve #100 and stored in a desiccator.

Solvent Evaporation Method:

The accurately weighed amounts of drug and polymer were dissolved in sufficient quantity (60ml) of solvent blend to obtain clear solution. Dichloromethane and methanol in the ratio of 2:1 was used as solvent blend for PEG 6000. The solvent blend was removed by evaporation in a water bath at 45°C under reduced pressure. The resulting residue was then transferred to glass desiccators and dried under vacuum to constant weight. The dried product was powdered and sifted through Sieve #100 and stored in a desiccator prior to use.

Estimation of etoricoxib

A quantity of solid dispersion equivalent to 100 mg of Etoricoxib was accurately weighed and dissolved in 0.1 N HCl in 100 ml. An ultraviolet (UV) Spectrophotometric method based on the measurement of absorbance at 234 nm in 0.1 N HCl was developed and used for the estimation of Etoricoxib. The method obeyed Beer's law in the concentration range of 0-10 mcg/ml where concentration of standard solution was assayed repeatedly (n = 6).

Dissolution rate study:

The dissolution rate of Etoricoxib as such and from its Solid Dispersions was studied using Disso 2000, Lab India 8-station Dissolution rate test apparatus with a paddle stirrer. The dissolution rate was studied in 900ml of 0.1 N Hcl containing 1 % SLS. Sodium lauryl sulphate was added to the dissolution fluid to

maintain sink condition. Etoricoxib (90 mg) or its solid dispersion equivalent to 90 mg of Etoricoxib, with speed of 50 rpm and temperature of $37 \pm 1^{\circ}\text{C}$ were used in each test samples of dissolution medium (5 ml) were withdrawn through a filter (0.45μ) at different time intervals, suitably diluted and assayed for Etoricoxib by measuring absorbance at 234 nm. The dissolution experiments were conducted in triplicate.

RESULT AND DISCUSSION

All the solid dispersions prepared were found to be fine and free flowing powders. Low SD and C.V (<2%) in the percent drug content values indicated that the drug content was uniform in a batch of solid dispersion in all the cases. The drug release profile was studied in 0.1 N Hcl containing 1% S.L.S. Sodium lauryl sulphate was added to the dissolution medium to maintain sink condition during dissolution rate study. The dissolution profiles of various physical mixtures and sold dispersions were shown in Fig. 1.

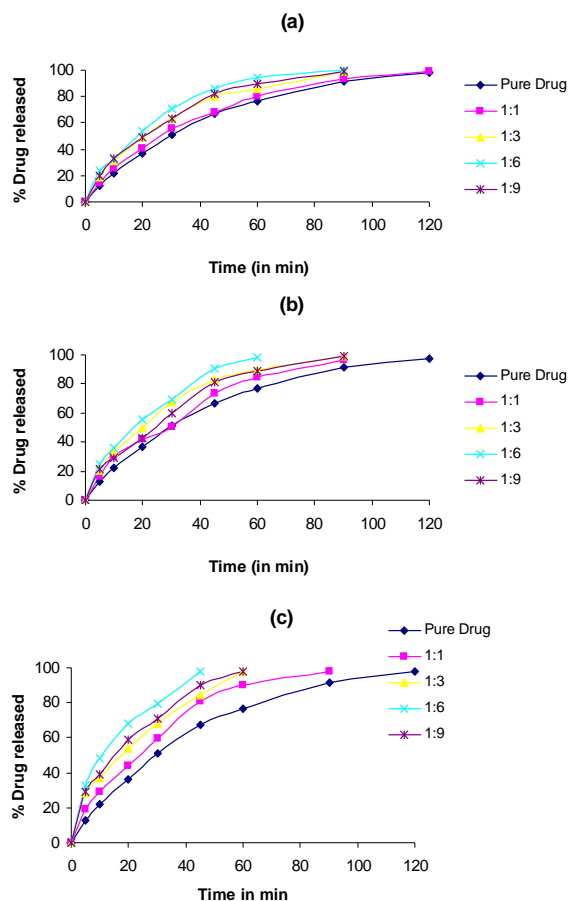


Fig 1: Dissolution profiles of Etoricoxib from PEG 6000 Solid Mixtures prepared by (a) Physical mixing (b) Kneading technique (c) Solvent evaporation.

All the solid dispersions showed marked enhancement in the dissolution of drug as compared to plain drug powder, the dissolution rates are in the order of SD>P.M>Pure drug, and is

clearly evident from the T_{50} , DE_{20} and DP_{10} values of pure drug, physical mixture and its solid dispersions. Shown in Table 1.

Table 1: Dissolution parameters of various Etoricoxib:PEG 6000 Solid dispersions prepared:

Product	*Percent Dissolved In 10 (min)	* T_{50} (min)	* DE_{20} (%)	* K_1 (min ⁻¹)	*r
ETORICOXIB	-	> 60	20	-	-
ETORICOXIB-PM					
1:1	25.76	26.20	22.58	0.0449	0.9598
1:3	31.29	21.1	31.12	0.0469	0.9537
1:6	32.12	16.12	33.56	0.0654	0.0737
1:9	33.30	25.20	28.62	0.0452	0.9454
ETORICOXIB-KM					
1:1	27.68	26.5	24.62	0.0502	0.9824
1:3	33.76	20.50	30.10	0.0446	0.9663
1:6	35.72	17.8	33.86	0.0482	0.9771
1:9	28.78	24.10	27.12	0.0497	0.9724
ETORICOXIB-SE					
1:1	28.92	11.50	25.12	0.0612	0.9683
1:3	37.0	17.10	31.18	0.0697	0.9830
1:6	47.98	10.00	43.72	0.0854	0.9848
1:9	38.92	20.7	27.12	0.0852	0.9598

DP_{10} = Percent drug dissolved in 10 minutes, T_{50} = Time taken for 50% dissolution
 DE_{20} = Dissolution efficiency at t=20 minutes, K_1 (min⁻¹) = First order rate constant.
 (n=3). r = correlation coefficient (first order). * = Average of 3 determinations.

It is clear that the dissolution of Etoricoxib has enhanced considerably from PEG 6000 solid dispersions compared to dissolution of plain drug. The reason for the poor dissolution of pure drug could be poor wettability and agglomeration of particles. And it can be seen that the dissolution of Etoricoxib increases with increase in PEG 6000 up to 1:4 ratio of drug: PEG 6000. Further in case 1:6 ratio, no marked increase in dissolution was observed. This might be due to complete dispersion of drug with PEG 6000 at 1:4 ratio. The dissolution of Etoricoxib as such and prepared solid dispersions followed First order kinetics. The dissolution rate constants (k_1) were calculated from the slopes of the first order linear plots of the dissolution data. Dissolution efficiency (DE_{20}) values based on the dissolution data were calculated according to Khan (Khan et al., 1975). T_{50} (Time taken for 50% dissolution) values were recorded from the dissolution profiles .Fig .2.

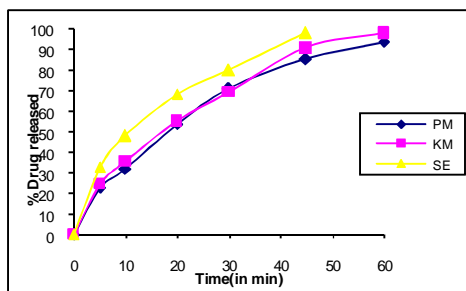


Fig.2: Comparison between dissolution profile of Etoricoxib: PEG 6000 1:6 ratios. Prepared by different methods:

PM=Physical Mixture

KM=Kneading Method

SE=Solvent Evaporation Method

This PEG 6000 solid dispersion prepared by solvent evaporation technique with Etoricoxib: PEG 6000 1:4 ratio was showed maximum dissolution rate with higher values of DP_{10} , DE_{20} and T_{50} than the SDs Prepared with other methods. This increase in the dissolution rate may be due to increase in drug wettability, solubilization of the drug by the carriers and possibility due to reduction in the drug crystallinity.

CONCLUSION

From the above studies, it was concluded that the SD technique has been shown as successful approach to improve the dissolution rate of Etoricoxib. The method and the amount of carrier used to play an important role in the enhancement of dissolution rate. CXB: PEG 6000 1:4 Solvent evaporation method exhibited higher dissolution rate than the corresponding solid dispersion.

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